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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/645,816	08/20/2003	Charles R. Cantor	25491-2408B	7901

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FISH & RICHARDSON, PC
P.O. BOX 1022
MINNEAPOLIS, MN 55440-1022

EXAMINER	
LU, FRANK WEI MIN	
ART UNIT	PAPER NUMBER
1634	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	02/01/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/645,816	CANTOR ET AL.	
	Examiner	Art Unit	
	Frank W. Lu	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 October 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,12 and 15-18* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,12 and 15-18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *11/03 and 12/03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Response to Amendment

1. Applicant's response to the office action filed on October 10, 2006 has been entered. The claims pending in this application are claims 1-3, 12, and 15-18. Rejection and/or objection not reiterated from the previous office action are hereby withdrawn in view of the response filed on 1-3, 12, and 15-18.

Specification

2. The disclosure is objected to because of the following informalities: (1) since now case 09/880,988 is US Patent No. 6,660,229, applicant is required to update this information in the first sentence of the specification; (2) There are Figures 1a to 1e, 5a and 5b, BRIEF DESCRIPTION OF THE FIGURES only describes Figures 1a, 1b, and Figure 5; (3) although DESCRIPTION OF THE FIGURES describes that Figure 6d is a set of sequences consistent with the graph shown in Figure 6c (see the specification, page 13, lines 15-25), since Figure 6c contains 2181 nucleotides (6094-3913) while Figure 6d only has 98 nucleotides, it is unclear how Figure 6d is a set of sequences consistent with the graph shown in Figure 6c; and (4) Figure 5a contains a nucleotide having more than 10 bases. However, DESCRIPTION OF THE FIGURES related to Figure 5a does not describe this nucleotide or there is no SEQ ID NO for this nucleotide in Figure 5a.

Appropriate correction is required.

Claim Objections

3. Claim 15 is objected to because of the following informality: there should be a period in the end of the claim.

Appropriate correction is required.

Claim Rejections - 35 USC § 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

5. Claims 1-3, 12, and 15-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Koster (US Patent No. 5,547,835, published on August 20, 1996) in view of Monforte *et al.*, (US Patent No. 5,965,363, published on October 12, 1999).

With respect to claim 1, Koster teaches methods for identifying nucleotides at one or

more base positions in a plurality of target nucleic acid molecules. By determining the mass difference of each nucleotide, a sequence of a target nucleic acid can be determined by the identity of each nucleotide base. Koster teaches each of the four different nucleotides has a unique mass (column 10, lines 9-12), and "through determination of the molecular weights of the four base-specifically terminated fragment families...the molecular weights of the four specifically terminated fragment families can be determined simultaneously by MS [mass spectrometry].., by running one reaction having all four chain-terminating nucleotides .... comparison of the mass difference measured between fragments with the known masses of each chain-terminating nucleotide allows the assignment of sequence to be carried out" (column 5, lines 13-31).

Regarding method step I, Koster teaches "the invention utilizes the Sanger sequencing strategy," wherein the Sanger sequencing method is the amplification and synthesis of a target sequence with DNA polymerases and the incorporation of complementary dNTPs and ddNTPs (column 1, lines 6167, through column 2, lines 1-8). Koster also teaches the incorporation of mass-matched and chain terminating nucleotides. Koster teaches "an amplification of the mass increment in mass-modifying the extended DNA fragments can be achieved by either using an equally mass-modified deoxynucleoside triphosphate (i.e. $dNTP^1$, $dNTP^2$) for chain elongation alone or in conjunction with the homologous equally mass-modified dideoxynucleoside triphosphate...ddNTP," wherein the superscript number indicates the position of the mass-modified nucleotide position (column 18, lines 22-31; and column 16, lines 63-67 through column 17, line 1).

Although Koster does not use the nomenclature "mass-matched," Koster uses the term "weight" as analogous to mass. Koster teaches mass spectrometry "weighs" individual molecules by ionizing them in vacuo and making them "fly" by volatilization under electric and magnetic fields, and said ions "follow trajectories depending on their individual mass (m) and charge (z) .... mass spectrometry has long been part of the routine physical-organic repertoire for analysis and characterization of organic molecules by the determination of the mass of the parent molecular ion" (column 5, lines 41-49). In view of Koster's teachings of "mass" and "weight," it is interpreted that the terms are interchangeable.

Regarding method step 2, Koster teaches calculating mass shifts of the incorporated nucleotides. Koster teaches mass shifts by the comparison of each nucleotide to that of a reference, wherein each nucleotide has a known weight, and the known target sequence has a calculated mass, wherein each incorporated nucleotide is compared to said reference (column 14, lines 53-67 through column 15, lines 1-7, Table 1 and Figure 6). Koster teaches the "correlation of calculated molecular weights...and their experimentally-verified weights .... The molecular weight difference between two adjacent peaks can be used to determine the sequence," wherein the weight is measured in daltons (column 14, lines 67 and 68 through column 15 lines 1-5).

With respect to claim 2, Koster teaches "the use of mass-modified nucleoside triphosphate as chain elongators...for Sanger DNA... sequencing," wherein the mass-modified nucleotides are have identical mass-modified weights (column 17, lines 16-19 and column 18, lines 21-25).

With respect to claim 3, Koster teaches mass-matched nucleotides wherein it includes deoxyinosine triphosphate (dITP) (column 15, lines 66-67 through column 16, lines 1, and in

view of claims 12 and 14) and deoxyinosine triphosphate dITP (column 15, lines 66-67 through column 16, lines 1-3; Figures 8A and B, and in view of claims 11 and 12).

With respect to clam 12, Koster teaches mass-matched chain terminating nucleotides. Koster teaches ddNTPs "have each been mass-modified so as to have molecular weights resolvable from one another" (column 10, lines 35-41).

Koster does not disclose that the target nucleic acid molecules are polymorphic or mutant sequence variants of a gene as recited in claims 1, 15, and 17 wherein the difference in sequence between the variants is a single nucleotide polymorphism as recited in claim 16 and the difference in sequence between the variants is an insertion or a deletion as recited in claim 18.

Monforte *et al.*, teach to screen nucleic acids for polymorphisms by mass spectrometric techniques (see abstract and columns 4-8) wherein the polymorphisms include point polymorphisms, insertions and deletions (see column 21, lines 44-63).

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to have performed the methods recited in claims 1 and 15-18 wherein the target nucleic acid molecules are polymorphic or mutant sequence variants of a gene and the difference in sequence between the variants is a single nucleotide polymorphism or an insertion or a deletion in view of the prior art of Koster and Monforte *et al.*. One having ordinary skill in the art would have been motivated to do so because Monforte *et al.*, have successfully screened nucleic acids for polymorphisms by mass spectrometric techniques (see abstract and columns 4-8) wherein the polymorphisms include point polymorphisms, insertions and deletions (see column 21, lines 44-63) and performing the method of claim 1 using a different starting material as the target nucleic acid molecules, in the absence of convincing

evidence to the contrary, would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made.

Furthermore, the motivation to make the substitution cited above arises from the expectation that the prior art elements will perform their expected functions to achieve their expected results when combined for their common known purpose. Support for making the obviousness rejection comes from the M.P.E.P. at 2144.06, 2144.07 and 2144.09.

Also note that there is no invention involved in combining old elements is such a manner that these elements perform in combination the same function as set forth in the prior art without giving unobvious or unexpected results. *In re Rose* 220 F.2d. 459, 105 USPQ 237 (CCPA 1955).

Response to Arguments

In page 6, third paragraph bridging to page 10, second paragraph of applicant's remarks, applicant argues that "[B]ecause Koster does not disclose any methods that include calculating a mass shift from a period, Koster does not anticipate the instantly claimed method Claim 1, nor any claims dependent thereon, including newly added Claims 15-18".

This argument has been fully considered but it is not persuasive toward the withdrawal of the rejection. Since it takes time for calculating the differences between the calculated molecular weights of 13 DNA fragments and the experimental molecular weights of 13 DNA fragments (see column 15, Table 1), Koster does disclose calculating a mass shift from a period as recited in claim 1.

Double Patenting

6. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or

improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ormum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

7. Claims 1-3 and 15-8 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-40 of U.S. Patent No. 6,660,229. Although the conflicting claims are not identical, they are not patentably distinct from each other because the examined claims in this instant application is either anticipated by, or would have been obvious over, the reference claims. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ormum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969). Although claims 1-3, 12, and 15-18 in this instant application are not identical to claims 1-40 of U.S. Patent No. 6,660,229, claims 1-40 of U.S. Patent No. 6,660,229 are directed to the same subject matter and fall entirely within the scope of claims 1-3, 12, and 15-18 in this instant application because the content of U.S. Patent No. 6,660,229 indicates that a target nucleic acid refers to a nucleic acid of interest in a sample having a particular mutation or polymorphism (see column 10, lines 14-20) such as a single

nucleotide polymorphism, an insertion and deletion (see column 12, lines 18-42) and chain terminated nucleotides can be mass-matched (see column 6, lines 24-36). In other words, claims 1-3, 12, and 15-18 in this instant application are anticipated by claims 1-40 of U.S. Patent No. 6,660,229.

Response to Arguments

In page 10, third paragraph bridging to page 12, last paragraph of applicant's remarks, applicant argues that claims 1-3 have been amended and claim 12 in this instant case is identical to claim 12 of U.S. Patent No. 6,660,229 which is directed to a different method.

This argument has been fully considered but it is not persuasive toward the withdrawal of the rejection because, although claims 1-3, 12, and 15-18 in this instant application are not identical to claims 1-40 of U.S. Patent No. 6,660,229, claims 1-40 of U.S. Patent No. 6,660,229 are directed to the same subject matter and fall entirely within the scope of claims 1-3, 12, and 15-18 in this instant application since the content of U.S. Patent No. 6,660,229 indicates that a target nucleic acid refers to a nucleic acid of interest in a sample having a particular mutation or polymorphism (see column 10, lines 14-20) such as a single nucleotide polymorphism, an insertion and deletion (see column 12, lines 18-42) and chain terminated nucleotides can be mass-matched (see column 6, lines 24-36).

Conclusion

8. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

9. No claim is allowed.

10. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center. The faxing of such papers must conform with the notices published in the Official Gazette, 1096 OG 30 (November 15, 1988), 1156 OG 61 (November 16, 1993), and 1157 OG 94 (December 28, 1993)(See 37 CAR § 1.6(d)). The CM Fax Center number is (571)273-8300.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Frank Lu, Ph.D., whose telephone number is (571)272-0746. The examiner can normally be reached on Monday-Friday from 9 A.M. to 5 P.M.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla, can be reached on (571)272-0735.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

January 5, 2006

FRANK LU
PRIMARY EXAMINER